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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,571	10/11/2005	Charles M. Rice III	56029-54474	4463

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EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,571	RICE III ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/28/05 and 6/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-38 are pending in the application.

Priority

2. It is noted that this application appears to claim subject matter disclosed in prior Application No. 60/426256, filed November 13, 2002.

A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c).

A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35

U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on September 28, 2005, and June 23, 2006 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Specification

4. The specification is objected to for containing referring to sequences without also identifying them by the sequence identifier assigned to them in the sequence listing as required by 37 CFR 1.821(d). See, pp. 12 (lines 7-9), and 25 (Table I). The examiner would like to bring the applicant's attention to the following excerpt from MPEP §2422.03:

> 37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences regardless of whether a given sequence is also embedded in the text of the description or claims of an application. This requirement is also intended to permit references, in both the description and claims, to sequences set forth in the "Sequence Listing" by the use of assigned sequence identifiers without repeating the sequence in the text of the description or claims. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO: 23" is permissible and the fragment need not be separately presented in the "Sequence Listing." Where a sequence is embedded in the text of an application, it must be presented in a manner that complies with the requirements of the sequence rules.

The applicant is therefore required to amend the specification to comply with 37 CFR 1.821(d).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 10-13, 19-36, and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are drawn to methods of producing a cell line permissive for HCV replication, and to cell lines produced thereby. The claims require the provision of a step comprising the culturing of cells that comprise replicating HCV RNA. It is not clear what is being required by these claims. In particular, it is not clear if the claims are

requiring that the provided cells actually include replicating HCV RNA, or if the cells merely include HCV RNA that is capable of replication. Clarification of the claim language is required.

It is suggested that the claims be amended to require an additional step between steps (a) and (b) of selecting for cells in supporting HCV RNA replication.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for the production of a cell line permissive for HCV replication comprising the culturing of cells comprising a replicating HCV RNA, selecting of cells in which the HCV RNA replicates, and curing the cells of HCV replication, does not reasonably provide enablement for methods of producing cells permissive for HCV replication wherein the cells of the respective steps (a) are infected with or comprise HCV RNA which is merely capable of replication. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary,

(2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

In the present case, the claims are broadly drawn to either methods of producing cell lines permissive for HCV replication comprising curing cells that have been either infected by HCV, or comprising replicating HCV RNA of the HCV or HCV RNA, or on cells so produced. It is noted that the present application defines cells to be permissive when the cell "supports HCV replication at a frequency that is greater than that of the cell or cell line from which it was derived." Page 2, lines 13-16. Thus, the claims broadly read on the production of cells, or cells produced by, the curing of cells infected with HCV or containing replicating HCV RNA, but where there is no requirement for a step of selecting such cells, and curing the cells with any anti-viral agent.

The claims are rejected because the claimed methods read on merely infecting or transfecting a cell with HCV RNA and curing the cells of the RNA, without also requiring selection of cells in which the HCV RNA is actually capable of replicating. In addition, claims 1-9, 16, 17, and 37 are also rejected for exceeding the scope of enablement because these claims read on methods wherein cells are not transfected with a replicating HCV RNA, but are infected with an HCV virus. These claims are rejected because the teachings of the application do not provide an enabling disclosure for such a method.

With respect to the first, more general, basis of rejection, the application provides support for the claims through demonstrating the making of HCV permissive cells. The disclosed method involves the provision of cells that have been transfected with an HCV replicon, selecting for cells in which that replicon actually replicates, and curing those cells of the HCV RNA. See e.g., page 7, Example 1; and page 14, Example 9 (each teaching the selection of cells wherein the replicon is undergoing replication through the use of the G418 resistance gene for curing).

The teachings in the art also indicate that the methods for the production of HCV permissive cell lines requires both a provision of cells comprising HCV replicons (i.e. HCV RNA capable of replicating) and the selection of cells wherein the HCV RNA is actually undergoing replication. See e.g., WO 02/059321, page 14 (stating that "Replicon enhanced cells are initially produced by selecting for a cell able to maintained an HCV replicon, and then curing the cell of the replicon). Thus, the teachings of the application and the art indicate that, to produce HCV permissive cells, the cells need not only be cured from the presence of the HCV RNA, but prior to the curing, need also to be selected for the actual ability of the replicon to be replicated in (and therefore maintained by) the cell.

With respect to claims 1-9, 16, 17, and 37, it is noted that the application provides no demonstration of the claimed method, or of any cells resulting from such a method. Moreover, the teachings of the art indicate that infections of cells generally results in only transient and inefficient infection, and that such infection did not result in a useable replication. See e.g., Sheehy et al., J Viral Hepat 14: 2-10, at 2-3. The reference indicates that as of several years after the filing date of the present application HCV infection of cells has yet to provide information as

to the replicative cycle of HCV, and indicates that the use of molecules clones (such as the HCV replicons-replicating RNAs- of the other claims in the application) so far presents the best source of developing useful models of HCV replication in vitro. Id., at page 8 (Conclusions). It is noted that a single clone of HCV has been isolated that is able to replicate in culture. See e.g., Lindenbach et al., PNAS 103:3805-09. However, the teachings in the art do not demonstrate that the cells in which this clone is able to replication become more permissive for replication of HCV in general. In view of the teachings of the art indicating significant complexity and unpredictability in the art regarding the replication of HCV from cells infected with HCV virus, the fact that models of replication based on such have not proved useful (state of the prior art), and the lack of any demonstration or evidence that the method of the present application has overcome the problems faced in the art and would lead to the successful development of An HCV permissive cell line, these claims are rejected as lacking an enabling disclosure.

9. Claims 16, 17, and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical

> and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

Claims 16, 17, and 37 read on cells permissive for HCV that are produced by infecting cells with an HCV virus, curing the cells, and identifying sublines of the cured cells that are permissive for HCV. These claims are rejected as lacking written descriptive support for the cells. Claims 18, 33-36, and 38 read on HCV permissive cells produced by the curing of cells transfected with replicating HCV RNAs (i.e. replicons). These claims are rejected because the application provides insufficient written descriptive support for the full scope of the cells that may be so produced.

In the present case, the application has claimed cells that may be produced by indicated methods, wherein the cells are identified according to a functional characteristic (their permissiveness for HCV replication). The application discusses the Huh 7.5 cells (although it does not provide adequate descriptive support for these cells as they have not been identified in such a manner that those of skill in the art would be capable of identifying such cells- e.g., by deposit), which have the indicated functionality. However, these cells were produced by a method involving the curing of Huh cells transfected with an HCV replicon.

Claims 16, 17, and 37 require that the cells be produced through curing cells infected with HCV. There is no demonstration that the same cells would result from these two methods. Thus, the disclosed Huh 7.5 cells do not represent a species of the cells of claims 16, 17, and 37.

With respect to claims 16, 17, and 37, because the application does not provide any species of the claimed genus of cells, the only descriptive support provided for such cells is the description of the functional activity of the cells. Such does not provide adequate support for a genus of claimed products. See e.g., Eli Lilly 43 U.S.P.Q.2d at 1406. See also, University of Rochester v. G.D. Searle & Co, 69 U.S.P.Q.2d 1886, at 1893 (CAFC 2004, indicating that the finding in Eli Lilly that the functional identification of compound is insufficient to provide descriptive support is not limited to genetic materials). Moreover, while the application also provides a method by which the cells may be produced, such also fails to provide adequate descriptive support for the claimed cells. See e.g., University of Rochester, 69 U.S.P.Q.2d at 1895. Thus, as the present application provides neither a representative number of species (in this case, no representative species), nor identifies the claimed cells through any means other than by function, the claims are rejected as lacking adequate written description support to demonstrate possession of the cells of claims 16, 17, and 37.

With respect to claims 18, 33-36, and 38, it is noted that the Huh 7.5 cell line is an exemplary species of the claimed genus. However, the present claims read on any HCV permissive cell line that may be produced by the claimed methods. It is noted that the methods are not limited to the use of any particular cell line, and infect implicitly read on the use of non-human and non-hepatic cells. See e.g., claims 29-31 (each narrowing the claims until claim 31 reads on only human hepatic cells, whereas claim 30 reads on any human cell, and claim 29 on

any vertebrate cells). It is noted that the present application indicates that other types of cells have been infected by HCV. However, the art indicates that efficient HCV replication is not seen in such cells. See e.g., Sheehy (supra.) at page 8. Moreover, even with respect to the replicon system, as of the time of filing efficient replication had been established only in the human liver cell line of Huh cells. See e.g., Lanford et al., Virology, 293: 1-9, at page 3 (right column). The art therefore provides evidence of uncertainty in the ability of those in the art to establish efficient HCV replication in non-Huh cell lines. It is noted that the MPEP indicates that where there is uncertainty in the operability of species other that those disclosed, the disclosed species may be found to be inadequate for establishing written descriptive support for a claimed genus. See e.g., MPEP 2163 II.3(a)(ii) (quoting In re Curtis, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004) as stating "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed.") As the present application provides an example of only an Huh cell-derived line that is permissive for HCV, and provides no evidence that the claimed method would be capable of producing HCV permissive cells from other cell lines, and in view of the teachings in the art indicating uncertainty as to the ability of other cells lines to permit HCV replication, the indicated claims are rejected as claiming a genus of HCV permissive cells beyond that for which sufficient written descriptive support has been provided.

Claim Rejections - 35 USC § 102-

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 10-15, 18-36, and 38 are rejected under 35 U.S.C. 102(a) as being anticipated by Blight et al. (J Virol 76: 13001-14- of record in the IDS of September 2005). These claims are drawn to methods for the production of a cell line permissive for HCV replication comprising culturing cells transfected with replicating HCV RNA, curing the cells through treatment with an anti-HCV drug (e.g.- interferon), and identifying sublines of the cured cells that are permissive for HCV replication. The claims also describe cells that may be so produced.

Blight teaches a method for the production of cell lines permissive for HCV replication. In particular, the reference shows the transfections of cells with HCV replicons comprising either the wild-type or cell-adapted sequences of the con1 HCV strain according to GenBank AJ 238799. Page 13002. The reference indicates that the transfected cells were cultured, then cured of the replicons through treatment with interferon, and that the cured cells were then tested for permissiveness (i.e. the identification of sublines permissive for HCV replication). Pages 13003-04. The reference therefore anticipates the claimed methods, and the cells produced by the methods.

It is noted that the reference has a publication date after the filing date or provisional application 60/426,256. However, as the present application does not contain proper reference to this prior application as required for a priority claim under 35 U.S.C. 119(e). Priority to the provisional application has therefore not been awarded.

12. Claims 10-15, 18-36, and 38 are rejected under 35 U.S.C. 102(e) as being anticipated by De Francesco et al. (WO 02/059321). These claims have been described above.

Like the Blight reference above, De Francesco also teaches methods for the production of HCV permissive cells by transfecting cells with an HCV replicon, curing the cells, and determining the permissiveness of the resulting cells. See e.g., Pages 22 and 31. The reference teaches that the cells may be initially transfected with either wild-type replicons, or replicons comprising one or more adaptive mutations; and teaches the use of replicons comprising the S2204I adaptive mutation. Pages 14 and 28. The reference also teaches cells resulting from the claimed methods. See e.g., page 31 (lines 14-19). The reference therefore anticipates the indicated claims.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Z. Lucas/
Patent Examiner, AU 1648